DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Claims 15-26 are presently pending for examination.

3. Applicant's filing of an Appeal Brief on 12/10/2008 is noted, Appellant's arguments with respect to the enablement rejection of claims 15-26 are addressed below.

4. The instant application claims priority back to 10/17/1997.

Response to Amendment

5. Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn.

Claim Rejections - 35 USC § 112

6. Claims 15-26 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling to "engender a biological response" in a mammal comprising the administration of a polyamide nucleic acid oligomer comprising a neutral amide backbone, and comprising a sequence that is fully complementary to said target nucleic acid, or having a single mismatch to the target nucleic acid does not reasonably provide enablement for practicing the claimed methods comprising the administration of a polyamide nucleic acid having more than one nucleotide that is not complementary to the target nucleic acid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

7. Applicant's arguments filed 06-19-09 have been fully considered but they are not persuasive.

8. Applicants traversed the instant rejection on the grounds that the numerous working examples provided within Applicant's specification demonstrate that a person of ordinary skill in the art could have made and used the claimed invention to engender a biological response in a mammal.

9. The examiner agrees that the specification as filed and the multiple Declarations filed under 37 CFR § 1.132 demonstrate the *in vivo* administration of multiple specific PNA oligomers targeting a variety of mRNA targets, wherein a sequence specific biological response was detected after *in vivo* administration of the PNA oligomer. However, Applicants have not addressed the rejection set forth in the prior Office Action to the extent that the instant claims have been amended to recite the administration of polyamide nucleic acid oligomers, "[w]herein said polyamide nucleic acid oligomers contain ***a sequence*** complementary to a target nucleic acid present in said mammal," the experimental data set forth in the Declarations filed in the related applications are not commensurate in scope with the claims of the instant claims. The scope of the instant claims can be interpreted as encompassing polyamide nucleic acid oligomers comprising a sequence that is not fully complementary to the target nucleic acid, i.e. comprising a partial complementary sequence to the target, or comprising an undefined number of mismatches.

10. According to Nielsen et al. (1993) PNA do not bind to its target nucleic acid when the PNA contains more than one mismatch to its target sequence. Therefore, to the

extent that the claimed methods, which comprise administration of PNA oligomers that contain ***a sequence*** complementary to the target nucleic acid, i.e. wherein an undefined number of mismatches are encompassed by the PNA oligomer, Applicant have not provided sufficient guidance for practicing the full scope of the claimed invention.

11. Moreover, Applicant's own specification provide a list of problems known to be associated with the use of polyamide nucleic acid oligomers at the time of filing of the instant application, see for example the following passage taken from page 2 of the specification as filed:

"Recent strategies devised to improve cellular uptake of PNA oligomers involve conjugating other molecules to PNA sequences. Specifically, conjugating a small peptide sequence that binds the insulin-like growth factor 1 receptor (IGF1R) to a PNA oligomer increases cellular uptake of labeled PNA sequences by IGF1R-expressing cells, whereas conditions using unconjugated PNA sequences or cells lacking IGF1R show ***negligible cellular uptake*** (Basu S. and Wickstrom E., *Bioconjugate Chem.* 8:481-488 (1997)). These results suggest that conjugating receptor ligand molecules to PNA oligomers can increase cellular uptake; *however, the ability of these receptor ligand-conjugated PNA oligomers to influence biological activity once inside the target cells remains unknown.* Further, PNA oligomers will gain entrance only into ceils expressing that particular targeted receptor. ***Thus, an appropriate ligand molecule would have to be designed and coupled to PNA oligomers for each cell type of interest. In addition, the level of receptor expression can influence the permeability of ligand-conjugated PNA oligomers.***"

The instant claims broadly read on the administration of a polyamide nucleic acid oligomer of undefined structure and modification, and further comprising an undefined degree of complementarity to the target nucleic acid. However, Applicant's own specification states that in order for PNA oligomers to gain entrance into cells, an appropriate ligand molecule would have to be designed and coupled to the PNA oligomer for each cell type of interest. Applicants have not provided sufficient guidance and/or instruction that would have allowed the skilled artisan following the teachings in the specification as filed to practice the full scope of the claimed invention without further undue, and unpredictable experimentation to design the appropriate ligand

molecule to conjugate to the PNA oligomers in order to achieve cellular uptake into each cell type of interest, and furthermore achieve a sufficient concentration of PNA oligomer into each cell type of interest in order to produce the desired biological response.

Applicants do not clearly define how the polyamide nucleic acid oligomers of the instant claims structurally differ from the prior art PNA oligomers that are known in the art to have negligible cellular uptake and require conjugation to a ligand specific for a particular cells type in order to achieve cellular uptake and produce a biological response. Other than the use of the specific PNA oligomers according to the present invention, Applicants have not provided clear evidence that their disclosed experimental results using the particular PNA oligomers described in the specification as filed, can be achieved using any generic polyamide nucleic acid oligomer as recited in the instant claims.

The claims remain rejected for the reasons set forth above.

Claim Rejections - 35 USC § 102

12. Claims 15-25 remain rejected under 35 U.S.C. 102(e) as being anticipated by Buchardt et al. (US 2002/0146718).

13. Applicant's arguments filed 06-19-09 have been fully considered but they are not persuasive. Applicants traversed the instant rejection on the grounds that "[A]t no point does the Buchardt et al. reference disclose the successful *in vivo* administration of a PNA oligomer to engender a biological response in a sequence specific manner."

Contrary to Applicant's assertions, and absent evidence to the contrary, since Buchardt et al. teach the general method of administering PNA oligomers in a mammal, wherein said PNA oligomer is complementary to a target nucleic acid, absent evidence to the contrary, the PNA oligomers of Buchardt et al. would possess the same characteristics as those set forth in the methods of the instant claims.

Conclusion

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Smith whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Epps-Smith/
Primary Examiner, Art Unit 1633